REMARKS

Reconsideration of the patentability of all of the pending claims of the above identified patent application is solicited.

Claims 11-20, that were previously withdrawn from consideration in this application, have been canceled because they are directed to a non-elected invention. The cancellation of these claims is not a disclaimer of the subject matter thereof. Applicants reserve the right to file one or more division applications directed to the subject matter of these canceled claims.

A petition to extend the response period for one month, to expire July 13, 2001, is being filed herewith. It is believed that the one month extension of time petitioned for is sufficient to maintain the pendency of this application. However, if additional time is required, kindly consider this to be a petition therefore. The fee required by the attached petition is also attached hereto and filed herewith. It is believed that this fee is correct. However, if the fee is incorrect, kindly charge any deficiency, including any fee that may be due for further extensions of time, or credit any overage to the undersigned attorneys' deposit account 07-1337.

Applicants acknowledge the fact that the examiner has withdrawn all objections to this application under 35 USC 112. The remaining rejections are all under 35 USC

102 and 103. The fact that the examiner has made all of these remaining rejections final is noted. With due respect, the final rejections extant in this application are traversed.

The instant invention is based on a novel set of compounds and the novel uses that have been found for these compounds. The instant novel set of compounds are targeted chimeric toxins that have been made by genetic engineering techniques. That is, the compounds of this invention are the products of fusing, at the cDNA level, a cell targeting moiety encoding GnRH and a cell killing moiety. The cell targeting moiety segment of these new compounds has the ability to recognize cells bearing gonadotropin releasing hormone binding sites. The cell killing moiety segment of these new compounds is a toxin that has the ability to kill cells bearing gonadotropin releasing hormone binding sites.

The two segments of the instant claimed compounds of this invention are ligated together. They are not chemically coupled by conventional chemical reaction techniques through intermediates that have had reactant moieties attached thereto. The instant claimed compounds are made by a distinctly different method than are the allegedly similar chemical compounds disclosed in the prior art. Indeed, because they are made by a different method, in this specific case, the claimed compounds are clearly different from the chemical compounds disclosed in the prior art. This point will be further discussed below. Additionally, as will also be further discussed below, the compounds of this invention have different utility and operating behavior as compared to the reported behavior and utility of the prior art chemical compounds that have been asserted to

anticipate the instant claimed compounds. This too shows that the instant claimed compounds are not the same as, and therefore not anticipated by, the chemical compounds of the prior art.

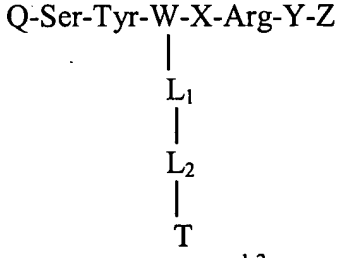
The examiner has correctly noted that the same compounds made by different methods are not patentably distinct from each other. If the exact same compounds are produced by different preparatory schemes, the later one is anticipated by the earlier one and is therefore not patentable. However, if the same reactants are joined together in a different manner so as to produce **different** resultant compounds, the earlier one does not anticipate the later one. Even more importantly, if the reactant compounds are not exactly the same, and the preparative methods are different as well, it should be clear that there is no possibility of an anticipation reaction being proper. The key question in evaluating the patentability of compounds is whether they are indeed the same as, or obvious in view of, other compounds that were in the prior art prior to the advent of the instant invention.

The predicate to a rejection of the patentability of certain compounds, such as the rejection made by the examiner in the instant application, that is allegedly based upon an anticipation theory and asserted to be supported by one or more reference(s), is that the same reactants are reacted together in the prior art as in the instant invention, and that therefore, the same products will necessarily result, even though the method of assembly of the instant claimed compounds is clearly difference from the method of reacting the prior art chemical compounds. While that is certainly a valid statement in its general

application, it does not apply to the instant situation. In the instant matter, the starting materials used to make the compounds of this invention are different from the reactants that are employed to make the chemical compounds in the references.

The examiner has alleged that the instant claimed compounds are anticipated by disclosures of the Nett et al. and the Lombardo et al. published PCT applications. Both of these references disclose chemically conjugated toxins of **functionalized** analogs of GnRH **chemically coupled** to a cell killing molecule such as Pseudomonas exotoxin. The functionalized analogs of GnRH are not the same as the GnRH reactant of the instant invention and, therefore, the products produced by the chemical reaction of these analogs with Pseudomonas exotoxin are **different** from the genetically engineered products being claimed herein that are made by ligation, at a cDNA level, of an analog of GnRH, that is not functionalized, with a cell killing moiety as claimed herein. Functionalization by the prior art introduced linking moieties into the reacting molecules, and the products disclosed in the references are the chemical reaction products of these modified moieties, having linking elements incorporated therein, with certain cell killing moieties.

Reference is made to the disclosure on page 10 of the Lombardo reference where it shows the linking moiety to be attached to the GnRH molecule at the 6 position:



where Q is PyroGlu-His-Trp, N-acetyl-4-Cl-Phe^{1,2}-Trp, or 3-indolylproprionyl

By way of contrast, the instant claimed compounds are not made by conventional chemical conjugation reaction through a linker, but rather by genetic engineering techniques. In the insatnt invention, the analog of GnRH is a modification at the 6 position where tryptophan has been substituted for the glycine of the naturally occurring GnRH making the genetically engineered molecule (fragment) look like:

NOT IN CLAIMS

GnRH----------→ $PE^{(PE40/PE66)}$

1 2 3 4 5 6 7 8 9 10

Met Glu His Trp Ser Tyr Trp Leu Arg Pro Gly

CATATGGAGCACTGGTCCTATTGGCTGCGCCCTGGA xxxxxxx

Neither segment of the final molecules of this invention is functionalized to add linkers as in the prior art, nor are the moieties that result in these segments conventionally conjugated to form the final product. It should therefore be immediately apparent that the compounds of the references are different from the compounds of this invention. The differences are well characterized by the methods of making the specific claimed compounds, especially the fact that the GnRH analog reactants are different in the prior art than they are in the instant claimed invention. These differences in starting moieties alone are sufficient to avoid the anticipation rejection that the examiner has entered.

Reference is particularly made to US patent 5,378,688 which is a parallel patent to the cited Nett et al. PCT '799 publication. In column 8, lines 7 et seq., this patent discloses modifying GnRH-A molecules by introducing amino acids at the 6 position. It further discloses modifying the GnRH molecule at the 10 position to introduce amino functionality at that position. There is disclosed the use of hetero-bifunctional bridging

moieties that are used to connect, or conjugate, the now modified GnRH molecule to the toxin. Thus, it should be clear that these resulting compounds are different from the compounds being claimed herein because the instant claimed product compounds do not have such modifications and linking elements. Rather, they have been made by genetic engineering techniques that do not require, or avail themselves of, such linking modifications.

The Rusieki et al. reference is entirely analogous to the disclosure of the Nett et al. reference in regard to the reactant molecules that are employed. Therefore, it too does not disclose the same compounds as are being claimed herein. The Lombardo et al. reference is similarly not pertinent to an anticipation rejection for the same reasons.

The examiner has stated that "The method in which the targeted fused chimeric toxins is produced is immaterial to their patentability." "...determination of patentability is based on the product itself" and not on the method by which the product is made. In re Thorpe is cited to support this position, and applicants cannot disagree with either the comments or the citation.

However, it is also clear that a consideration of the methods by which compounds are made, and especially the reactants that are employed, will often give an indication of whether the product compounds are likely to be the same or different. That is, while a different method of manufacture will not make the prior art chemical compounds patentable again, it may well tell you that the reaction products are, or are not, the same

compounds. In the instant case, reaction products of A and B are not the same as reaction products of an analog of A and B with a linker there between. The instant products, that are obtained by genetic engineering and fusion of complementary DNA's for GnRH and PE, have a single primary protein structure; **no linkers**. Thus, the examiner's position cannot sustain an anticipation rejection in this specific case.

In addition to these cited references not supporting an anticipation based rejection because they disclose different chemical compounds than the compounds that are being claimed herein, it should be clear from the instant disclosure, compared to the disclosures of the references, that the instant compounds behave differently from, and have different utilities than, the chemical compounds of the references. Differences in behavior are indicia of differences in chemical structure. The Court of Appeals has often held that a compound is not characterized by it name or proposed structural formula alone, but is also characterized by its physical and chemical properties. That is, differences in properties of allegedly identical compounds indicate that they are not identical but are different compounds. This too shows that an anticipation rejection of the instant claims is not supported by the references.

The references' disclose conjugated toxins that are reported to be active as sterilizing agents, in treating sex hormone related diseases and as anti-cancer drugs (see column 6 of the '688 patent for example). On page 13 of the '799 PCT reference, it is stated that, "Applicants have found that GnRH conjugations of the types noted in Table II above are particularly effective in causing the toxic compound T to be specifically

targeted to the gonadotropin-secreting cells of the anterior pituitary gland. Indeed, they are the only cells to which the gonadotropin-releasing hormone portion of the conjugate will bind." It is clear from this quote that the instant compounds are quite different from the chemical comppounds of the prior art because they can bind non-hormone dependent cells.

The physiological effects of the chemical compounds of the prior art result from the specific structures of chemical compounds containing linkers. These chemical compounds are made by binding of the targeted conjugated toxin to an **analog** of the GnRH receptor that is present in gonadotrophs (i.e., LH releasing cells) of the pituitary gland. This binding results in a chemical compounds that kills the cells bearing a GnRH receptor. This causes the pituitary gland to lose its ability to produce luteinizing hormone (LH) and follicle stimulating hormone (FSH). This not only provides a chemically castrating effect, but it has an adverse effect on several sex-steroid dependent tumors. These tumors respond to such hormonal manipulation so that their growth is controlled.

The targeted chimeric toxins of the instant invention target other cells than the chemical GnRH toxin conjugates. The instant claimed targeted chimeric toxins bind to, and have cytotoxic activity with respect to, colon carcinoma cells as well as carcinoma cells of the kidney, breast, ovaries, cervix and liver. This shows that the compounds of this invention can selectively bind to and target a site that is not a GnRH receptor, but rather is another, different GnRH binding site that has previously been unknown. This newly discovered site has not yet been cloned or characterized. It was not known prior to

this invention how to target cells having a GnRH binding site which were not targeted and bound by the chemical toxin conjugates of the prior art.

The targeted chimeric toxins of the present invention can and do bind directly to tumor cells and kills them. The anti-tumoral activity results from a direct killing or cytotoxic effect on the tumor cells rather than via indirect chemical castration as in the prior art. The highly cytotoxic activity of purified GnRH-PE66 and GnRH-PE40 on several colon carcinoma cell lines is most surprising because these cells do not have the known and cloned human pituitary GnRH receptor. The prior art does not disclose or suggest this. Reference is here made to page 18, example 9 and figure 8 of the instant application for support for this substantially different utility.

There is strong evidence that the targeted chimeric toxins claimed in the instant application are chemically and physically different from the chemical compounds that have been disclosed in the prior art. Specifically, they are distinct from the chemical toxin conjugates shown in the '799 and '751 PCT publications. Even though genetically engineered immunotoxins are generally conventional in the art of targeted conjugates, the instant chimeric toxins are not immunotoxins and the targeting moiety has not been derived from an anti-body type molecule. It is most surprising that a genetically engineered moiety derived from GnRH can target and bind to a cell site that is not the known and cloned human pituitry GnRH receptor.

Neither of the primary references suggests a recombinant fusion molecule comprising GnRH as the cell targeting moiety. Even if a recombinant fusion protein of GnRH and PE was prepared and tested on gonadotrophs to see whether the targeted chimeric toxin is cell specific cytotoxic, any cytotoxic activity found on cells that bear no GnRH receptor would have been considered to be "unspecific" cytotoxoic activity and a failure. Consequently, there was little or no motivation to investigate the seemingly unspecific cytotoxic effect of genetically engineered GnRH-PE toxins. Prior to the present invention, the GnRH binding site was not known and therefore it cannot have been regarded as obvious to use the instant claimed recombinant toxins to target and kill cells bearing this GnRH binding site that had not previously been known to exist.

It has been pointed out above that the properties of a compound are very important in determining if one compound is the same as some other compound. How a compound behaves is a good measure of its identity. The chemical compounds of the prior art target gonadotrophs of the pituitary gland that are expressing a GnRH-receptor. The molecules of the instant invention target a GnRH binding site that is different from the human pituitary GnRH binding site. This new binding site is expressed on adenocarcinomas. Reference is here made to the first three new publications listed in the attached IDS.

Reference is also made to the fact that the targeted chimeric toxins of the instant invention constitute a new class of chimeric toxins targeting a short sequence of 10 to 30

amino acids. This fact too, leads to the conclusion that the instant compounds are different from those disclosed in the prior art.

These different characteristics also make it clear that the references do not anticipate the claims of the instant application. It is urged that the rejections of paragraphs 8, 9, and 10 be withdrawn.

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In paragraph 11 of the outstanding action, claims 3, 4 and 21 of this application have been rejected as being directed to subject matter that would have been obvious to a person of ordinary skill in this art at the time that this invention was made considering the combined disclosures of the cited Nett et al. PCT application and the cited Chaudhary et al. article. The examiner's position asserts that it would have been *prima facie* obvious to produce a targeted fused chimeric toxin comprising the GnRH disclosed by Nett et al. and the mutated form of PE or PE40 as taught by Chaudhary et al.

The disclosure of the Nett et al. reference has been amply discussed above. The essential matter concerning this reference is that it employs linkers or other molecular modifications to cause a GnRH analog to become chemically bonded to a toxin, such as PE. Substituting the "mutated form of PE or PE40 as taught by Chaudhary et al." for the toxin disclosed in the Nett et al. reference, would **not** result in the compounds being claimed herein. Therefore, no *prima facie* case of obviousness has as yet been raised by the examiner. On that basis alone, the obviousness based rejections made by the examiner must fail. In the absence of *prima facie* obviousness, the burden of proof does

not revert to the applicants. Unless the examiner raises *prima facie* obviousness, applicants have no burden of going forward with additional evidence to show unobviousness.

However, even if it is assumed, *arguendo*, that the examiner has made out a case of *prima facie* obviousness, the evidence in the instant application clearly shows that the compounds claimed in the instant application are unobviously different from the compounds disclosed in the prior art. The unobvious behavior and utility of the compounds claimed herein overcomes any possible *prima facie* obviousness that the examiner might raise.

The chimeric GnRH toxin conjugates (including their linkers) of the two PCT publications act by attacking gonadotrophs of the anterior pituitary gland that are expressing the GnRH receptor. These cells are the only cells to which the chemically conjugated GnRH toxin conjugates of the references bind.

In contrast to that, the targeted chimeric toxins of the instant invention bind via a different binding site. The binding sites through which the toxins of the instant invention bind are different from the human pituitary GnRH receptor. As stated above, this new binding site has not yet been cloned and characterized. Heretofore, it was only known how to target cells having a GnRH binding site. It was not previously known how to target cells having a GnRH binding site that are not targeted and bound by the chemical toxin conjugates of the prior art. In contrast to the manner in which the toxins of the

prior art operate, the targeted chimeric toxins of this invention bind directly to tumor cells and kill them. The anti-tumoral activity of the compounds of the instant invention results from the direct killing of, or cytotoxic effect on, the tumor cells themselves rather than indirectly through chemical castration. The instant specification has ample data to show that purified GnRH-PE66 and GnRH-PE40 are highly cytotoxic on several colon carcinoma cell lines. (Please see page 18, Example 9 and Figure 8 of the instant specification) This is most surprising because these cells do not have the known and cloned human pituitary GnRH receptor.

It is therefore urged that the examiner reconsider his final rejection and withdraw all of the remaining rejections. Allowance of all of the claims is solicited.

Respectfully submitted,

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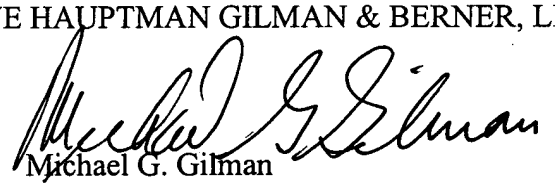

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